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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,900	11/08/2000	Moon Jong Noh	54751-015	9053

7590 01/24/2003

Attn: Joseph H. Kim, PhD
SQUIRE, SANDERS & DEMPSEY L.L.P.
14th Floor
801 S. Figueroa St.
Los Angeles, CA 90017-5554

EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/24/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,900	NOH ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002 and 08 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Applicant's arguments filed 7-30-02, paper number 9, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 6-12 and 16-22 have been canceled. Claims 1-5 and 13-15 are under consideration in the instant application.

Specification

The rejection regarding new matter in the amendment filed 10-9-01, paper number 6, under 35 U.S.C. 132 is withdrawn in view of the amendment of the specification back to its original form.

Claim Objections

The objection to claim 9 has been withdrawn because the claim has been canceled.

1. The "and" in claim 15 should be --or--.

Claim Rejections - 35 USC § 112 - new matter

2. Claims 1-5 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation of treating osteoarthritis with chondrocytes transfected with TGF-β1 or BMP is new matter (claims 1 and 13). Support has not been provided and cannot be found.

The phrase "transfected/transduced" is new matter. Support has not been provided and cannot be found (claims 1, 4, 5 and 13).

Failure to provide support for future amendments will be considered non-responsive.

Claim Rejections - 35 USC § 112 - enablement

3. Claims 1-5 and 13-15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transfecting fibroblasts with DNA encoding TGF-β1 operably linked to a promoter, transplanting the transfected fibroblasts into a joint space of a mammal such that expression of TGF-β1 occurs resulting in generating hyaline cartilage, does not reasonably provide enablement for using chondrocytes encoding TGF-β1 or BMP to treat arthritis or regenerate any connective tissue as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The specific combination of vector, cell and modes of delivery required to target a desired tissue and regenerate tissue *in vivo* is unpredictable. Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the

long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

More specifically, at the time of filing Naughton taught transplanting foreskin fibroblasts to a site of cartilage damage in the presence of scaffolding and regenerating cartilage, suggested

transfecting the cells with a vector encoding TGF-β1 and suggested delivering the cells intraarticularly (Naughton, claim 1; col. 10, line 58; col. 4, line 65; col. 13, line 60 - col. 16, line 33; col. 2, line 56 and col. 18, lines 8-42 which discusses administering the cells to joints that have damaged cartilage). Ikeda taught administering a vector encoding TGF-β1 intraarticularly to obtain TGF-β1 expression (pg 1667, col. 1, 3rd para.; pg 1669, col. 2). van Beuningen taught TGF-β1 administered intraarticularly generates articular cartilage (pg 307, col. 1, "intraarticular injections"; pg 308, col. 1, "stimulation of articular cartilage"). The art did not teach how to use fibroblasts or TGF-β1 to regenerate ligaments or tendons. The art did not teach how to use BMP to regenerate cartilage. The art did not teach how to use osteoblasts or chondrocytes to regenerate cartilage or any other connective tissue.

The specification does not enable using the instant invention to treat osteoarthritis (claim 1). Arthritis in humans causes a diverse T-cell population response against not just collagen or one antigen, but a large number of undefined antigens in the arthritic joint (Fox et al., July 1995, Am. J. Med., Vol. 99, pgs 82-88; pg 87, col. 1, para. 1; pg 84, col. 4, para. 1). The specification demonstrates the invention in rabbits having cartilage defects made with a knife (pg 29, line 7). These rabbits are not an art accepted model for osteoarthritis; nor do the rabbits correlate to osteoarthritis. While arthritic joints require cartilage regeneration, removing cartilage reflect with a knife does not reflect the complex immune response in an arthritic joint. The specification does not teach how damaging cartilage with a knife reflects the diverse T-cell response against the undefined antigens in the arthritic joint as taught by Fox et al. The specification does not provide

adequate guidance to regenerate cartilage in an arthritic joint because the cells administered may be attacked by the immune system and may not target the damaged area of cartilage.

The specification does not enable using chondrocytes transfected with DNA encoding TGF-β1 or BMP to regenerate cartilage or connective tissue. Specifically, the specification does not correlate the results obtained using TGF-β1 to BMP-2, -3, -4, -5, -6 or -7 such that cartilage would be regenerated. Nor does the specification correlate the function of TGF-β1 to BMP-2, -3, -4, -5, -6 or -7 such that cartilage could be regenerated. While the specification suggests using BMP (page 11, line 9), the activities and functions of TGF-β1 and BMPs vary. The specification does not provide the structural features or functional activity of any BMP required to regenerate cartilage or any other connective tissue. The specification does not correlate the results obtained using fibroblasts to chondrocytes. The specification does not correlate the structure or function of fibroblasts and chondrocytes. Without such guidance, it would require one of skill undue experimentation to use different cells and DNA to regenerate connective tissue in view of the state of the art at the time of filing which only taught fibroblasts encoding TGF-β1.

Given the unpredictability in the art taken with the guidance provided in the specification, it would have required one of skill undue experimentation to use chondrocytes transfected with DNA encoding TGF-β1 or BMP to regenerate hyaline cartilage or any desired connective tissue as broadly claimed.

Applicants argue the specification suggests using chondrocytes and BMP on pg 5 and 9. Therefore, applicants believe the specification explicitly allows for the use of chondrocytes to

regenerate cartilage following the same or similar method as using fibroblasts applying well known molecular biological techniques (pg 6 of response). Applicants argument is not persuasive. The rejection is not based on making transfected cells but how to use them to treat disease. Applicants have not provided any correlation between the results in the specification or the art at the time of filing and chondrocytes encoding TGF-β1 or BMP as claimed.

Applicants argue regeneration of hyaline cartilage can be thought of as *de facto* treating osteoarthritis because osteoarthritis is caused by the mechanical wearing of the cartilage. Applicants argue no immuno-rejection is seen by the inventive procedure. Therefore, applicants conclude that the specification enables the claims. Applicants argument is not persuasive. Applicants argument is not persuasive. Cutting cartilage with a knife as disclosed does not correlate to osteoarthritis because it does not take into account the autoimmune response that causes osteoarthritis. The mechanical wearing that causes osteoarthritis is a result of the autoimmune system destroying the cartilage in a joint. Applicants model is not an art recognized model of osteoarthritis and does not correlate to osteoarthritis for reasons of record.

Claim Rejections - 35 USC § 112 - indefiniteness

The rejection of claim 8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn because the claim has been canceled.

4. Claims 1-5 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "transfected/transduced" is unclear. The metes and bound of "transfected" and "transduced" cannot be determined. Therefore, the metes and bounds of cells that are either "transfected" or "transduced" cannot be determined. The distinction between transfecting and transducing cannot be determined.

The phrase "chondrocyte cells" is indefinite. Chondrocytes are simply referred to as chondrocytes, not chondrocyte cells.

Claim Rejections - 35 USC § 102

The rejection of claims 16-21 under 35 U.S.C. 102(b) as anticipated by Agrawal (1995, Ind. J. Exp. Bio., Vol. 33, 708-709) has been withdrawn because the claims have been canceled.

Claim Rejections - 35 USC § 103

The rejection of claim 16-22 under 35 U.S.C. 103(a) as being unpatentable over Agrawal (1995, Indian J. Exp. Biol., Vol. 33, pg 708-709) has been withdrawn because the claims have been canceled.

The rejection of claims 1-5 and 13-15 under 35 U.S.C. 103(a) as being unpatentable over Naughton (US Patent 5,842,477, Dec. 1, 1998) in view of Ikeda (Sept. 1998, J. Rheumatol., Vol. 25, pages 1666-1673) and van Beuningen (Sept. 1998, Osteoarthritis and Cartilage, Vol. 6, pages

306-317) has been withdrawn because the references do not teach transplanting cells without scaffolding as newly amended.

Double Patenting

5. Claims 1-5 and 13-15 remain provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-22 of copending Application No. 09/702718. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Applicants willingness to file a terminal disclaimer in the letter sent 11-8-02, paper number 11, has been noted.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

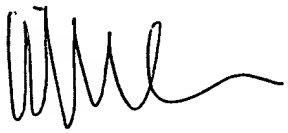
Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER